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# NUTRITION REVIEWS

## July 1951

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NUTRITION REVIEWS

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## CALORIC PRIORITIES IN PARENTERAL NUTRITION

Subsequent to the early work of R. Elman and D. O. Weiner (*J. Am. Med. Assn.* **112,** *796 (1939)*), in which an acid hydrolysate of casein with added tryptophan and cystine was given intravenously to maintain nitrogen equilibrium in man, a host of studies have appeared which confirm the discovery of the ability of the body to utilize amino acids administered parenterally, not only for energy purposes but in synthesis of new protein. At the same time, clinicians administering a liter or more of 5 per cent amino acids a day for one or two weeks to malnourished patients have all too frequently failed to observe a rise in serum albumin or, indeed, any clinical evidence that the patient was obtaining benefit from such therapy.

Unfortunately, the growing lack of confidence in parenteral amino acid preparations has resulted from lack of knowledge about certain elementary principles of nutrition. The fault does not ordinarily lie in the amino acid preparations but rather in the conditions under which they are used. Thus when amino acids fail to do their assigned job of building new protein, it is usually because of the nutritional environment in which they are given, not because of the preparation. Although this fact is well-known to most workers in the field of nutrition, there is an astonishing lack of information in the clinical world about the nutritional conditions under which amino acid utilization is optimal. Actually, the problem of amino acid utilization is inextricably entangled with that of caloric balance. Therefore, any physician who wishes to use parenteral amino acids successfully must at the same time concern himself with the patient's caloric intake.

In the animal organism energy requirements invariably take precedence over all other metabolic demands. Thus, in semi-starvation the ingested protein which would ordinarily be utilized for synthesis and replacement of body tissue is instead diverted in whole or in part to meet energy requirements. For proper use of parenteral amino acids there must at the same time be present an immediately available supply of calorigenic material. For maximal efficiency of amino acid utilization, the caloric and amino acid intake must be temporally integrated.

In contrast to this view is a statement by R. Elman (*Bull. N. Y. Acad. Med.* **20,** *220 (1944)*) suggesting that in an average sized adult, 100 g. of glucose per day added to the energy derived from metabolism of tissue fat enables the body to meet energy requirements without the necessity of gluconeogenesis from tissue protein. This estimate is based indirectly on data which show that on the fourth day of starvation a normal subject may excrete about 15.0 g. of nitrogen in the urine, while in the presence of a protein-poor, calorically adequate diet, 5 g. of nitrogen are excreted in the urine. The difference between excretion of nitrogen in total starvation and in protein starvation amounts to some 10 g. of nitrogen, therefore Elman calculated that in this instance, 62.5 g. (250 calories) of body protein was broken down and used for energy. The rest of the energy requirement was assumed to be supplied from tissue fat.

Later R. Elman, H. W. Davey, and R. Kiyasu (*J. Lab. Clin. Med.* **30,** *273 (1945)*) described nitrogen retention in the presence of an intake manifestly inadequate in calories, the energy deficit again being presumably made up by endogenous fat. In this instance, however, the nitrogen intake was extremely high, with a proportion of protein to carbohydrate of 4:1. Also, the studies were done using healthy dogs which, prior to the experiment, had been in a well-nourished state.

F. N. Schulz and E. Mangold (*Pflüger's*

*Arch. f. d. ges. Physiol.* **114,** *419 (1906)*) found that, while the fasting dog still possesses considerable depot fat, protein in the food is readily retained, even though the content of energy in the diet is less than the needs of the animal. F. A. Evans and J. M. Strang (*J. Am. Med. Assn.* **97,** *1063 (1931)*) studied a number of obese patients in considerable detail and found that on an intake of 445 calories and 58 g. of protein per day, these patients were brought into and kept in nitrogen equilibrium. According to A. Keys, J. Brozek, and their associates ("The Biology of Human Starvation," *Univ. of Minnesota Press, Minneapolis (1950)*), however, results obtained in obese patients on intakes low in calories and nitrogen are not comparable to those obtained in normal lean subjects during semistarvation. "Normal" individuals appear to require 2500 to 3000 calories a day in order to remain in nitrogen equilibrium on a diet containing 60 to 70 g. of protein.

There is then no disagreement about the importance of calories in making possible maximal utilization of dietary nitrogen. However, it apparently has not been clear that estimates derived from studies on obese individuals and animals with adequate stores of fat cannot reasonably be applied to the majority of patients who require prolonged parenteral feeding. Indeed, the amount of nitrogen excreted by a normal subject during early starvation in excess of his so-called "endogenous" level may well represent protein broken down to provide essential carbohydrate to the body. It does not follow that a comparable amount of dietary carbohydrate will be as efficiently utilized, nor does this represent the amount of carbohydrate which will ensure efficient utilization of dietary protein. Accordingly, one has no right to expect, when this small amount of metabolized body protein is replaced by an equivalent amount of dietary glucose, that body protein will be largely spared and that the balance of body energy requirements will be readily supplied from depot fat. And when the organism is depleted of fat, which is frequently the case in patients requiring parenteral alimentation, an abundance of exogenous calories must be supplied in addition to the "essential" carbohydrate in order to ensure effective utilization or sparing of nitrogen.

The problem in parenteral nutrition, then, is not one of finding better amino acid preparations; it is rather one of administering calorigenic materials in quantities sufficient to guarantee effective utilization of the amino acids.

Unfortunately, it is not so easy to administer calories parenterally as it is to decide upon their worth. Parenteral glucose alone cannot solve the problem for several reasons. First, because when it is given in hypertonic concentrations, it is irritating to veins, frequently producing thrombophlebitis. More importantly, it has been shown that the maximum speed of dextrose administration which does not produce appreciable glycosuria ranges from 0.5 to 0.75 g. per kilogram of body weight per hour. Thus to provide from this source 2000 calories to a man weighing 70 kg. would ideally require about ten hours of continuous intravenous administration. This would entail use of volumes of water which could easily embarrass the circulatory status of many patients. And since amino acids are metabolized at an average rate of 15 g. per hour, it is clear that administration of them in adequate amounts alone requires considerable time and a large volume of fluid. Administration of hydrolysate preparations containing appreciable quantities of polypeptides is associated with a large loss of the polypeptides in the urine (H. N. Christensen, E. L. Lynch, and J. H. Powers, *J. Biol. Chem.* **166,** *649 (1946)*). Accordingly, preparations of this kind will require even more time and more fluid as a condition of their utilization.

Attempts have been made to provide more calories by parenteral means in a more efficient manner. The calorigenic preparations that have excited greatest contemporary in-

terest are: (a) intravenous fat emulsions; (b) invert sugar solutions; (c) ethyl alcohol preparations.

Parenteral use of fats and oils for caloric purposes has been discussed and sporadically studied experimentally for more than thirty years. There are good theoretical reasons for believing that emulsions of oil in water would constitute the best possible source of intravenous calories. Fat itself is calorically rich, with an energy value of 9 calories to the gram. Furthermore, fat particles do not exert an osmotic effect and therefore are not injurious to veins, even in high concentrations. Fat emulsions can be made at the physiologic pH. Parenterally administered fat is not excreted through the kidneys or into the gut; therefore none is lost during or after administration.

Despite these theoretical virtues, clinical use of emulsified fat for intravenous administration has not been possible until recently. However, within the last few years 15 per cent emulsions of coconut oil in water containing dextrose for isotonicity and stabilized with small amounts of phosphatide and co-stabilizer have been given in large quantities to patients requiring parenteral calories (E. M. Neptune, R. P. Geyer, I. M. Saslaw, and F. J. Stare, *Surg. Gynec. Obstet.* **92,** *365 (1951)*). Careful histologic studies on animals and on human autopsic material have failed to disclose evidence of irreversible damage from infusions of this kind. Evidence for utilization of the fat has been obtained using as criteria gain in weight, reversal of negative nitrogen and potassium balances due to insufficient calories, total carcass analysis for fat, changes in respiratory quotient, rise in blood ketones following fat administration, and lastly from radioactive tracer studies in which the $C^{14}$ of labeled fat administered intravenously was recovered in the respired carbon dioxide (Geyer, L. W. Matthews, and Stare, *J. Biol. Chem.* **180,** *1037 (1949)*).

Several problems still must be solved before a clinical fat emulsion can be made generally available. Of primary importance is the manufacture of a consistently pyrogen-free oil (*Nutrition Reviews* **9,** *163 (1951)*). Also, the present stabilizing system is not ideal since vasomotor disturbances are occasionally associated with its use. A mild hypochromic anemia apparently due to effects of the stabilizing system may occur following prolonged use of fat emulsions. Further studies on patients receiving fat emulsions for extended periods must be done before final evaluation of this material as a source of calories can be made. However, on the evidence so far adduced, fat emulsions seem to have all the characteristics necessary for solution of the caloric problem.

Invert sugar has recently attracted attention as a possible source of parenteral calories. It is prepared by hydrolysis of sucrose and is composed of equal parts of dextrose and fructose (levulose). Interest in it has been renewed since J. J. Weinstein (*Ann. West. Med. Surg.* **4,** *373 (1950)*) reported that invert sugar could be given intravenously to nondiabetic human subjects at a rate of 1.7 g. per kilogram per hour without appreciable loss in the urine.

Since the tonicity of invert sugar is approximately the same as that of a comparable concentration of dextrose, it is difficult to believe that a hypertonic solution of the preparation would be any less irritating to veins. Moreover, invert sugar in amounts adequate to provide daily energy requirements would still have to be administered along with excessive volumes of water. On the basis of Weinstein's data and, provided the fructose is efficiently metabolized, it would appear that the value of invert sugar lies primarily in the convenience associated with the increased rate, and therefore decreased duration, of administration. However, balanced against this apparent virtue is the fact that rapid intravenous injection of a large volume of fluid is not without hazard, particularly in patients with cardiovascular disease (*Nutrition Reviews* **9,** *173 (1951)*). Until further studies have been done opinion as to the value of invert sugar as a

source of parenteral calories superior to glucose must be reserved.

Lastly, the use of alcohol by the intravenous route is perennially mentioned as a possible solution to the calorie problem. Ethyl alcohol, when completely metabolized, has a caloric value of approximately 7 calories per gram (5.6 calories per milliliter). Use of it intravenously for pharmacologic purposes has been long known; parenteral use of it as a source of calories was described in 1939 by S. Mueller (*Surg. Clin. North America* **19,** *401 (1939)*). In 1945 D. C. Moore and M. Karp (*Surg. Gynec. Obstet.* **80,** *523 (1945)*) reported the successful use of intravenous alcohol in 5 and 10 per cent concentrations in the nutritional treatment of surgical patients suffering from inanition. At that time, they stressed the importance of exercising careful control over the rate of administration of the alcohol so that toxic symptoms might be avoided. Their work appeared to confirm the findings of E. Mellanby (*Brit. Med. Res. Com. Spec. Report* **31,** *1 (1919)*), who observed that the normal individual metabolizes approximately 10 ml. of alcohol in an hour, regardless of the blood alcohol level. Moore and Karp found that a higher incidence of vascular sclerosis followed use of the 10 per cent solution.

C. O. Rice, B. Orr, and I. Enquist (*Ann. Surg.* **131,** *289 (1950)*) reported on their experience with intravenous alcohol used in conjunction with glucose and amino acids in the parenteral feeding of surgical patients. They found that the optimal rate of administration for 60 ml. of alcohol mixed in a liter of 5 per cent amino acid-5 per cent glucose solution was about four hours. They were able, at this rate, to keep blood alcohol levels in the neighborhood of 100 mg. per cent, a level usually associated with only mild intoxication. Based on oxygen consumption studies, it was their belief that the alcohol tended to be utilized at a rate determined by the caloric requirements of the subjects. In one of their studies a 28 per cent increase in metabolic rate was associated with intravenous administration of alcohol.

When the alcohol was isocalorically substituted for glucose in the parenteral diet of a subject who had previously been in positive nitrogen balance, they found that a nitrogen deficit promptly ensued. On the other hand, when alcohol was used in combination with glucose, the supplementary calories derived from the intravenous alcohol appeared capable of sustaining a positive nitrogen balance.

There appears to be agreement that alcohol produces energy which cannot be "stored" in the sense that it does not form glycogen or fat. Its intermediate metabolism is imperfectly understood. Apparently it can be converted to acetate in the liver and possibly in the kidneys. It can then undergo further degradation through the tricarboxylic acid cycle, and is presumably utilized peripherally.

In evaluating the worth of alcohol as a source of calories, it is important to remember that the rate of its utilization does not exceed 10 to 15 ml. per hour. Therefore, its utilization is considerably slower than that of glucose. Its effect on veins is not well known. There is some clinical evidence suggesting that it may not be particularly traumatic to veins. If this is true, it may be added to solutions of dextrose and amino acids without a proportionate increase in the sclerosing property of the resulting mixture. Alcohol is not lost from the body to any appreciable extent; accordingly, its addition to glucose-amino acid preparations would not result in undue waste of calorigenic material. An important consideration in the use of intravenous alcohol is the need for constant supervision and control over the rate of its administration so that undesirable pharmacologic effects will not occur. Since its intermediate metabolism is still not well understood, it is not possible to evaluate it properly as a calorigenic substance. It is probable that as a nutrient its chief role will continue to be as a supplement to the caloric content of other parenteral preparations.

No discussion of priorities in parenteral nutrition can afford to omit reference to the nutritive value of the red blood cell. The work of G. H. Whipple (*Am. J. Med. Sci.* **203,** *477 (1942)*) indicates that in many anemic states, administered nitrogen is preferentially used in the regeneration of hemoglobin. Therefore, the task of replenishing the anemic patient's protein stores can be greatly assisted if his hematologic needs are at the same time satisfied.

In summary, parenteral nutrition will succeed only if the caloric demands of the patient who is unable to eat can be met, either parenterally or from his own stores. When such body stores are lacking, as is usually the case in chronic wasting diseases, caloric needs cannot be adequately met by the parenteral preparations now available. Accordingly, the need for a more effective intravenous calorigenic material is urgent. Fat emulsions plainly offer the only practical solution to this problem. It is to be hoped that the technical difficulties now preventing widespread use of them will soon be overcome.

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## BALANCE STUDIES ON VITAMIN $B_6$ IN MAN

Several studies on the disposition of vitamin $B_6$ in human subjects have appeared (*Nutrition Reviews* **7,** *215 (1949)*); in none of these, however, has a complete balance study of the vitamin and its known metabolites been made. A report of such a study by H. Linkswiler and M. S. Reynolds (*J. Nutrition* **41,** *523 (1950)*) is therefore of interest. Ten volunteers ate an all-vegetable diet providing a daily vitamin $B_6$ intake (depending upon the amount of diet ingested) varying from 0.53 to 1.21 mg. (average, 0.76 mg.) for different individuals. This was supplemented during the ten-day experiments with 0, 2, or 15 mg. of pyridoxine hydrochloride daily. Each individual served as his own control, the experimental periods being separated by an interval of two weeks during which the subjects ate a normal diet. Each of the ten-day periods was also preceded by a four-day "depletion" period during which an all-vegetable diet providing somewhat less vitamin $B_6$ than the basal diet was ingested. Complete collections of urine and feces were made for nine-day periods. Total vitamin $B_6$ (pyridoxine, pyridoxal, and pyridoxamine) was determined microbiologically with *Saccharomyces carlsbergensis*; 4-pyridoxic acid was determined fluorometrically by the method of J. W. Huff and W. A. Perlzweig (*J. Biol. Chem.* **155,** *345 (1944)*).

Results showed that 10 individuals with an average vitamin $B_6$ intake of 0.76 mg. per day excreted daily during the experimental period 0.71 mg. and 0.09 mg. of the vitamin in feces and urine, respectively, and 2.38 mg. of 4-pyridoxic acid in the urine. Urinary excretion of vitamin $B_6$ and its oxidation product, 4-pyridoxic acid, thus surpassed considerably the daily intake of the vitamin. If one adds fecal excretion to this, the total excretion surpasses the intake by about four times.

Three subjects fed 2 mg. of pyridoxine per day in addition to their basal diet (total average vitamin $B_6$ intake, 2.92 mg. daily) excreted a total of 4.6 mg. of vitamin $B_6$ and its metabolites daily, of which only 0.92 mg. was present in the feces. Again the output surpassed the intake. At the highest level of intake, 15.7 mg. per day, the total output fell to about 10.7 mg. of vitamin $B_6$ and 4-pyridoxic acid per day, of which only 0.81 mg. was in the feces. Administration of 12 g. of sulfasuxidine daily with the basal diet failed to decrease the excess of output of vitamin $B_6$ and pyridoxic acid over the intake.

The study confirms the following facts

indicated by previous investigators: (a) variation in the daily intake of vitamin $B_6$ has relatively little influence on the amount excreted in the feces (*cf.* C. W. Denko *et al.*, *Arch. Biochem.* **11,** *109 (1946)*)—it may be concluded that the excess of ingested vitamin over and above a constant proportion absorbed or synthesized and retained by the intestinal flora is completely absorbed by the host animal; (b) of the vitamin absorbed, by far the largest proportion (75 to 90 per cent in this study) eventually is excreted in the urine as 4-pyridoxic acid (*Nutrition Reviews, loc. cit.*); (c) at high levels of intake, less of the vitamin is excreted in known forms than is ingested (*Nutrition Reviews, loc. cit.*), the remainder apparently being excreted in unidentified forms, or oxidized within the body. In addition, the study strongly indicates that synthesis of this vitamin, presumably by the intestinal flora, may provide substantial amounts of vitamin $B_6$ for absorption by the human body. The authors suggest that such synthesis may explain the difficulties of W. W. Hawkins and J. Barsky (*Science* **108,** *284 (1948)*) in producing vitamin $B_6$ deficiency in man.

A few minor weaknesses of this study should be pointed out. It is not certain that the extraction procedures used for liberation of bound forms of vitamin $B_6$ prior to microbiologic determination suffice to free all of the vitamin present. If not, the amount ingested would be underestimated. On the basis of work to date, it is also not certain that the fluorometric method for 4-pyridoxic acid measures only this substance. The error, if any, would be particularly significant in basal urines from individuals not fed supplementary pyridoxine; hence, at low levels of intake the amount of this product excreted might be overestimated. Both errors would tend to produce a falsely high estimate of the negative balance. It may also be recalled that vitamin $B_6$ deficiency is difficult to produce in adult experimental animals, and failure to produce it in adult human subjects in relatively short experimental periods does not necessarily indicate that the needs for the vitamin are being wholly met by intestinal synthesis. Finally, by administration of vitamin $B_6$-deficient diets followed by test loads of tryptophan, L. D. Greenberg, D. F. Bohr, H. McGrath, and J. F. Rinehart (*Arch. Biochem.* **21,** *237 (1949)*) have supplied distinct evidence of a requirement for vitamin $B_6$ in human adults that apparently is not met by the amounts available for absorption from the lower intestinal tract. Further studies will thus be required to assess the importance of this vitamin in the diet under practical conditions of nutrition, and the extent to which the need for it can be supplied by the intestinal flora. The present study supplies distinctly valuable background information for such more detailed studies.

## AMPHETAMINE IN TREATMENT OF OBESITY ASSOCIATED WITH DIABETES

One of the health hazards associated with obesity is the much more frequent occurrence of diabetes mellitus than in individuals who are not overweight. This risk is greatest in persons of middle age or in later life. The factors associated with obesity which influence the occurrence of diabetes have not been precisely determined. However, loss of body weight by the obese diabetic may result in important gains in control of the disease. Carbohydrate tolerance may be improved with a decrease in insulin needs, or in occasional instances the use of insulin may be abandoned and the patient remain free of manifestations of the disease (*Nutrition Reviews* **3,** *142 (1945)*; **6,** *257 (1948)*).

In the attempt to control obesity, and to effect weight loss, a diet must be provided which meets minimum nutritional requirements but is low enough in calories so that

fat deposits within the body are burned. More important than simple provision of a diet is the obtaining of cooperation of the patient in strict adherence to the dietary regimen. It is in this regard that programs of weight reduction often fail. An understanding of the motivations of the patient and psychotherapy provide important assistances in therapy. Drugs have been sought and utilized which facilitate loss of body weight. Thyroid and anorexigenic substances are among those which have been used for these purposes (*Nutrition Reviews* **8,** *18 (1950)*).

A recent experience has been recorded in which anorexigenic drugs were administered in addition to a low calorie diet to effect weight reduction in obese diabetic patients (K. E. Osserman and H. Dolger, *Ann. Int. Med.* **34,** *72 (1951)*). The investigators had been unable to maintain adequate dietary control in a large group of obese patients with diabetes and had found it impractical or impossible to use psychotherapy in all patients treated in their clinic. For these reasons an evaluation of the effects of anorexigenic drugs was undertaken.

Fifty-five obese diabetic patients ranging from 20 to 70 years of age were in the group studied and were under observation for periods varying from eighteen to thirty months. Administration of insulin was required to maintain control of the diabetes in 31 patients. The disease was associated with essential hypertension in 30 patients. All of the patients had failed to adhere to a low calorie diet in earlier attempts to control obesity.

Each patient was placed on a diet of 1000 calories. The diet is not further described in the report. After several weeks on this diet, it was ascertained that in no patient had demonstrable reduction in weight been accomplished and no evidence of improvement of the diabetes mellitus was obtained. After this interval on dietary therapy alone, the anorexigenic drug, amphetamine sulfate, was added to the therapeutic regimen in doses of 10 mg. three times daily. The drug was first provided as D,L-amphetamine sulfate, "Benzedrine." Later the D-isomer, "Dexedrine," was substituted when it was found that 3 patients with hypertension had developed further increase in blood pressure while on D,L-amphetamine sulfate. There was no evidence that D-amphetamine in the doses given caused an increase in blood pressure in any of the patients. Similar depression of appetite was produced by both forms of the drug.

The patients were seen at fortnightly intervals and observations were made of weight, blood pressure and glycosuria. Fasting blood sugar values and/or glucose tolerance were determined in each of the patients at monthly intervals.

Thirty-six of the 55 patients lost more than 10 pounds of body weight during the period of restricted diet plus amphetamine. The greatest weight loss was 77 pounds in one individual. The data given do not state the periods of time in which these weight reductions occurred nor the relationship between degree of obesity and total loss in body weight. Despite use of the anorexigenic drug, 19 patients were unable to adhere strictly to the low calorie diet and as a result did not achieve a significant decrease in body weight.

The favorable effect of weight reduction on tolerance to carbohydrate in the obese diabetic patient was again demonstrated in these observations. Of 31 patients who required insulin at the initiation of this investigation, 15 were able to discontinue use of the hormone after significant loss of weight, and the insulin dosage was reduced in an additional 11 patients. The daily insulin requirement had been as great as 70 units per day in individuals who later found it possible to discontinue insulin. In addition, results of glucose tolerance tests done at monthly intervals in 28 milder diabetics who had not required insulin administration demonstrated improvement in tolerance in one-third of the group. Six of these patients

had normal tolerance to glucose after weight reduction.

Frequently clinical reports dealing with results of treatment of obesity do not extend observations beyond the period of dietary restriction or other treatment. Osserman and Dolger (*loc. cit.*) continued to follow the patients treated with amphetamine for a period of twelve months following discontinuance of the anorexigenic agent. It was found that 40 per cent of the patients regained body weight varying from 11 to 26 pounds; 41 per cent either maintained the weight achieved during the study or gained less than 10 pounds; 19 per cent of the patients continued to lose weight. It was also shown that of the patients who had discontinued insulin therapy, 50 per cent found it necessary to resume insulin administration within the period of a year. Four patients who had not previously used insulin required it as they regained weight following treatment with amphetamine.

Since the patients included in this study had unsuccessfully attempted weight control previously by use of a low calorie diet, the weight reduction and consequent improvement in diabetes may be attributed to use of amphetamine. This is further established by the fact that 40 per cent regained weight when the drug was stopped. It is perhaps disappointing that more of the patients were not sufficiently impressed with the health gains accruing from the regimen of weight reduction to continue a program of control.

Amphetamine has effects other than that of depression of appetite. Certain of these might seem to contraindicate its use in patients with diabetes. It has been demonstrated, for instance, that the drug may produce hyperglycemia and an increase in blood pressure. There was no evidence in the study discussed here that either D,L- or D-amphetamine sulfate had a direct effect on blood sugar levels. The D,L-isomer did produce an increase in blood pressure in three patients. In addition, two patients developed a generalized dermatitis, presumably as an effect of the drug. Some patients also complained of nervousness, palpitation and insomnia. The side reactions were on the whole relatively few, readily controlled, and without serious effects on the health of the patients.

The results observed in these patients cannot be claimed to be the direct effect of the anorexigenic drug. Rather, amphetamine, by producing depression of appetite, made it possible for patients to comply with and persist in a restricted diet. A more direct approach is for the physician to gain an understanding of the physiologic and psychologic motivations of the patient which have resulted in overeating and obesity. The patient must then be made to understand the nature of his problem and be stimulated to restrict his diet for purposes of health. It is only by such means that cooperation is achieved which will permit the patient not only to lose weight but also to maintain himself at near standard weight. Certainly this is the ideal and most effective approach in treatment. It has the disadvantage of being time-consuming, and more often than not tests the ingenuity of the therapist. However, the patient with diabetes must be seen frequently, educated in terms of his own care, and assisted in developing an awareness of his own nutritional needs and hazards. Better than most patients, he should understand and readily accept a regimen of dietary restriction which would modify and lessen the severity of his disease.

## ESSENTIAL FATTY-ACID DEFICIENCY IN MICE

All young animals thus far studied have been found susceptible to the dietary disease brought on by lack of the essential fatty acids, linoleic and arachidonic acids. Exter-

nal symptoms of the disease are fairly well-known and include skin disorders, scaliness of the feet and tail (in rats and mice), dermatitis, and dandruff. In rats, fatty livers and kidney lesions appear on autopsy.

In contrast to these readily demonstrable symptoms in the growing animal, symptoms of the deficiency are produced in mature animals only with great difficulty. V. H. Barki and co-workers (*Nutrition Reviews* **6,** *149 (1948)*), by starving adult rats to approximately one-half their normal weights, succeeded in producing deficiency symptoms on feeding a fat-free diet ad libitum to the emaciated animals. In actuality, of course, the deficiency was induced even in this case only by growth (albeit in mature animals) of the animals.

Because of these circumstances, a report by A. B. Decker, D. L. Fillerup, and J. F. Mead (*J. Nutrition* **41,** *507 (1950)*) describing the induction of a chronic deficiency state in mature mice due to lack of essential fatty acids is of interest. The diet used was composed of vitamin-free casein, sucrose, salts, and celluflour, with added fat- and water-soluble vitamins. To check the suitability of the diet, it was fed to two groups of young mice (initial weights about 10 g.), one of which also received corn oil ad libitum. Excellent growth of the animals receiving corn oil resulted, while in the fat-free group, after an initial period of rapid growth, the growth curve plateaued at weight levels much below that of the supplemented group. In this deficient group of young animals, the symptoms of acute essential fatty acid deficiency previously described in mice by E. A. White, J. R. Foy, and L. R. Cerecedo (*Proc. Soc. Exp. Biol. Med.* **24,** *301 (1943)*) were readily reproduced. These included loss of hair, dandruff, dermatitis, and scaliness and crustiness of the skin. Male animals appeared to be definitely more susceptible to the deficiency than female animals. They were smaller, and all eventually died, whereas the female animals, though in poor condition, survived even after four months on the diet. Supplementation of the deficient diet with corn oil led to growth and recovery of the surviving animals.

Having established the suitability of the ration, it was next fed to more nearly mature animals (average initial weights 20 g.). Fat-free and fat-supplemented groups in this case grew much more uniformly, although a slight growth advantage remained with the latter group. The deficient animals showed no external symptoms of essential fatty acid deficiency even after eight months on the fat-free ration, but rather appeared normal and healthy. The only signs of abnormality were an increased water consumption (also noted in acutely deficient young animals), and fatty livers. Experiments to follow possible blood changes during the deficiency soon demonstrated, however, that while control animals showed no ill effects from a small tail wound, and the wound itself rapidly healed, deficient animals behaved quite differently. In the latter the wounds failed to heal, the tails usually became necrotic and were lost, while the animals lost weight, began to show symptoms of acute fat deficiency, and finally died. Thus the deficient animals, although apparently normal in appearance, were wholly unable to cope with a slight stress which had no ill effects on the supplemented group.

To assess further the effects of stress, deficient female mice were mated to normal males of proved virility. Although little effect of the deficiency on the estrus cycle was noted, none of the matings resulted in pregnancies, and no young were born. Temporary weight increases were occasionally noted, and some of the animals subsequently showed symptoms of acute fatty acid deficiency. It is possible that both results were the consequence of temporary pregnancies which were not maintained.

Finally, various control and chronically deficient adult animals were exposed to 500 Roentgens of whole body x-irradiation. This

is slightly over the dosage which leads to 50 per cent mortality in stock animals. Eight of 9 animals fed the fat-free diet with corn oil ad libitum survived the treatment; only 2 of 17 animals fed the fat-free diet for seventy days before irradiation survived. The lethal effect of irradiation of the deficient group was not prevented by supplementation of the diet with corn oil following exposure to x-rays.

These interesting results not only extend our knowledge of fatty-acid deficiency, but provide an example of a type of nutritional deficiency in which superficial appearance is unchanged, but in which the resistance of the animal to several types of stress or injury has been markedly impaired. The possibility that pronounced differences in resistance of human individuals to various stresses may, in some cases, similarly have a nutritional basis even though recognizable signs of malnutrition are absent, is one which can not be excluded.

## EFFECTS OF STARVATION ON THE CENTRAL NERVOUS SYSTEM

There is a relatively large older literature on the anatomy of nervous tissues in starved men and animals. The studies agree that no significant macroscopic changes can be detected and that the brain loses very little in weight even under conditions of prolonged and marked caloric deficiency. In terms of microscopic analysis, it is impossible at present to arrive at a clear picture of the effects of starvation on nervous cells and their aggregates. The studies, of which relatively few were carried out in the last decade, lack consistency in the histologic alterations ascribed to starvation. Furthermore, there is an almost total lack of correlative studies which would provide a basis for a physiologic (functional) interpretation of the observed microscopic changes.

A well-designed and technically well-executed study on the effects of starvation on the central nervous system was carried out recently by C. N. Liu and W. F. Windle (*Arch. Neurol. Psychiat.* **63,** *918 (1950)*). It was undertaken in order to gain a valid picture of the histologic changes in starvation. This involved providing adequate control observations, using a sufficient number of animals, and employing improved technical methods of fixation and staining of the brain tissues. Attention was focussed on the effects of starvation on the nerve cell body rather than the nerve fibers, especially on the structures in the cytoplasm called Nissl bodies (or tigroid substance). The Nissl bodies are granular masses which may be stained with basic dyes and which give to the cell a striped (tigroid) appearance. They vary in size and number according to the functional state of the neurons and undergo disintegration (chromatolysis) when the functional state is impaired, *e.g.* as a result of injury.

In order to obtain data which would facilitate the interpretation of any histologic changes which might result from starvation, a group of guinea pigs was trained during the control period to run a simple maze. The animals were then retested after they recovered physically from the starvation stress, to determine whether the stress impaired the retention of the learned maze-running skill.

Healthy adult males were used as the experimental animals. Four control animals were fed a balanced diet ad libitum. On the average, they gained 84 g. in eleven days at which time they were killed as described below. All animals had free access to water and salt. The first experimental group consisted of 24 guinea pigs. These animals received no food for eight to sixteen days. In the 16 animals who died after the average period of ten days, the body weight decreased from 461 to 277 g. (an average

decrease of 40 per cent of the control weight). One to thirteen hours after death the brains were removed and fixed by immersion in formaldehyde. Eight animals were sacrificed after a starvation period of eleven days, with an average weight decrease from 424 g. to 240 g. (43 per cent decrease).

In these animals and in the control animals death was induced by perfusing through the heart an isotonic solution of formaldehyde containing acacia. The perfusion-fixation of tissues with formalin is a more physiologic approach than the technic used on animals which died naturally (H. Koenig, R. A. Groat, and W. F. Windle, *Stain Technol.* **20,** *13* (*1945*)). Before the start of perfusion the control animals were anesthetized with pentobarbital sodium. In the starved animals the perfusion was initiated at a time of collapse (loss of righting reflexes, convulsions, dyspnea, loss of sensations) and impending death. Selected sections of the brain were stained for Nissl bodies and for myelin sheaths.

The animals which died of starvation and whose brains were fixed by immersion in formaldehyde showed histologic changes similar to those described by earlier investigators. The sections stained lighter than those from the control animals and the experimental animals killed by the perfusion-fixation technic. Microscopically, there were marked diffuse neuronal changes in all parts of the brain, consisting of shrinkage and swelling of the nerve cells, clouding of the Nissl body patterns and in some instances complete chromatolysis, vacuolation of the cytoplasm, and enlarged perineuronal spaces. However, these changes, absent in animals on whom the perfusion-fixation technic had been used, were not due to inanition but must be interpreted as artifacts due to post-mortem changes and inadequate, delayed fixation. These artifacts may be observed in the brain of normal guinea pigs as early as one-half hour after death.

The brains of starved animals on which the perfusion-fixation technic had been used showed only minimal differences from those of the control animals. The glial cells, providing a supporting framework for the nerve cells, were not affected. At low magnification there was no difference in the intensity of staining or brilliancy of the color. Even the microscopic examination of the sections stained for myelin sheaths (the lipoid covering of the axons) showed no difference between the brains of the starved and control animals. The only differentiation appeared in the sections stained with thionine for Nissl bodies and even there the cytologic differences were anything but impressive.

The second group of 11 animals was placed on a semi-starvation diet, reduced to one-half or one-third of the normal ration (1 part of balanced diet plus 1 or 2 parts of celluflour). In weight the biscuits equalled the fully balanced diet normally eaten by animals of comparable size. After fifteen to forty days (average period of twenty-three days), their body weight decreased from 545 g. to 377 g. (a 31 per cent decrement). None of these animals died of starvation; each was killed by perfusion with the fixing fluid. With high magnification the same minor cytologic changes as observed in animals of the totally starved group were present. There was no correlation between the extent of the loss of body weight and the number of cells affected. The effect was perhaps slightly more pronounced in the semi-starved animals.

The third group consisted of 12 animals. Two served as controls, 4 died after seven to ten days of starvation. The remaining 6 received no food for eight to nine days, decreasing their body weight from 422 to 261 g. (38 per cent loss). During the control period they were trained to the point of perfection to run a single-alternation maze (R. F. Becker, *Quart. Bull. Northwestern Univ. Med. School* **20,** *318* (*1946*)). An attempt was made to retest the animals in the maze on the eighth day of starvation

but they were too weak, except for one animal who ran the maze ten times without error. When the animals were refed to a point of good bodily strength they were retested in the maze, on the fourteenth day after the beginning of the experimental period. There were no significant changes in the retention of the learned skill of running the maze and, consequently, no evidence of impairment of memory resulting from starvation.

The experimenters noted also the general activity of the animals while kept in their individual cages. The activity increased markedly in the early part (third to seventh day) of the starvation period. Later the activity began to decrease until they moved only very little, reaching finally a semi-comatose stage.

The relationship between gross bodily activity and "hunger," defined in terms of the number of hours of food deprivation, was studied quantitatively by P. S. Siegel and M. Steinberg (*J. Comp. Physiol. Psychol.* **42,** *413 (1949)*). The activity level was determined by recording the number of times the animal moved from one to the other end of an activity chamber which was divided by a light beam focussed on a photo-electric cell. Interruption of the beam closed a relay circuit which in turn activated an impulse counter (Siegel, *J. Psychol.* **21,** *227 (1946)*). The activity level of 60 male albino rats was determined under conditions of ad libitum food and water intake; the mean activity index was 16.8. When the animals were divided into four matched groups and their activity determined after twelve, twenty-four, thirty-six and forty-eight hours of food deprivation, the mean activity index increased to 29.0, 36.1, 36.5, and 39.3. Had the observations been carried beyond forty-eight hours of food deprivation, the decline in activity reported by Liu and Windle (*loc. cit.*) might have been confirmed. This pattern was seen in the rat earlier by W. T. Heron and B. F. Skinner (*Psychol. Record* **1,** *51 (1937)*), who studied not the general but a specific activity, namely, depressing a lever which brought about a periodic release of a minute portion of food. The rate at which the lever was depressed, recorded for one hour daily, continued to rise during the first five days of food deprivation. Subsequently, the number of responses began to decline and dropped finally to zero when the animals became too weak to move. The rise in general activity (locomotion) for a period up to four days was also observed by G. Wald and B. Jackson (*Proc. Nat. Acad. Sci.* **30,** *255 (1944)*).

## METABOLISM IN SHOCK

The recent paper of E. Shorr, B. W. Zweifach, R. F. Furchgott, and S. Baez (*Circulation* **3,** *42 (1951)*) brings new emphasis to the shock problem from the experimental standpoint, while simultaneously H. K. Beecher (*J. Am. Med. Assn.* **145,** *193 (1951)*) approaches the question from the therapeutic view. It seems noteworthy that the eminently practical schema for shock therapy outlined by Beecher, while extremely useful as a guide in the early care of seriously wounded patients, has not considered the possibility of what may be termed the chemotherapy of shock in the nutritional sense. It should be stressed that this statement does not constitute a reproof. It merely demonstrates that most of the workers interested in shock have approached the problem from hemodynamic aspects and these aspects have consequently come more to the fore in the thinking of surgeons who have had to deal with the condition of shock face to face.

Shorr's paper can be regarded as demonstrating a fairly clear connection between disturbances of hemodynamic control and tissue metabolism, since vasoexcitatory material and vasodepressor material (VEM

and VDM) have been shown to have their origin in tissue and to be markedly influenced as to their blood levels by the status of the animal as regards tissue oxygenation.

Whether or not VEM and VDM may be considered, at present, of prime importance in the causation of the gross manifestations of shock, the fact remains that their presence is an indication of serious tissue metabolic defects. If one is considering tissue metabolic defects in shock, perhaps it would be well to re-examine the series of papers which appeared during the years 1941 to 1945 by W. M. Govier, M. E. Grieg, W. E. DeTurk, and P. D. Lamson (*J. Pharmacol. Exp. Therap.* **72,** *317, 321 (1941)*; **77,** *40 (1943)*; **79,** *169, 240, 246 (1943)*; **81,** *164, 240 (1944)*; **83,** *220, 250 (1945)*). These studies demonstrated conclusively that one metabolic defect of considerable importance in shock is the breakdown of coenzymes of metabolic systems, in particular cocarboxylase, diphosphopyridine nucleotide, and alloxazine adenine dinucleotide. It was also shown that administration of relatively large amounts of vitamins can result in resynthesis of these molecules with concomitant increase in survival time of the shocked animals. It was of particular interest that animals which were fortified with large amounts of vitamins before bleeding did not go into shock by the usual pathologic standards, although they may have died of conditions resulting from sheer paucity of circulating red blood cells. Grieg was also able to show that apoenzymes as well as coenzymes are destroyed, thus giving an insight into the "irreversibility" problem, since one may agree that coenzymes may be rather more easily resynthesized than apoenzymes. The breakdown of coenzymes has been confirmed by B. Alexander (*J. Clin. Invest.* **23,** *259 (1944)*), and W. H. McShan *et al.* (*Am. J. Physiol.* **145,** *93 (1945)*), while F. L. Engel, M. G. Winton, and C. N. H. Long (*J. Exp. Med.* **77,** *397 (1943)*), by demonstrating the increase in blood amino acids in shock, confirmed the breakdown of apoenzyme protein if one assumes that the latter behaves as other protein in these conditions.

Some nutritionists have argued that vitamins can have no function if there is no deficiency of vitamins, and that therefore in shock, when the vitamin concentration of tissues remains as it was before shock, additional vitamins cannot be of benefit. The well-known fact should be stressed that most vitamins are only active when combined as coenzymes and that a coenzyme deficiency may exist even in the presence of an abundance of free vitamins. The reactions (which are enzymically catalyzed) resulting in coenzyme breakdown can conceivably be made to run in the direction of coenzyme synthesis, if large concentrations of free vitamins are used, whether this occurs by mass action or by inhibition of catabolic enzymes.

The logical termination of this argument can be presented as a provocative question: May we now consider shock to be a condition entirely brought on by metabolic failure and characterized by a multiplicity of mechanical failures caused by the metabolic one?

Willingness to answer this question affirmatively must then suggest that we have never saved a shocked patient by plasma administration alone, if the disorder has progressed to the stage of apoenzyme breakdown, and seldom if coenzymes alone are destroyed. In short, in this schema, plasma is excellent prevention, but not a cure. One must also consider what may be done in addition to plasma administration in shock therapy. Here one must consider that in all probability very little can be done for those patients whose apoenzymes are destroyed. Administration of vitamins in large doses, either combined with a blood substitute or separately, could conceivably be a beneficial factor in patients with coenzyme destruction. Clinical trial of such preparations would be of the utmost desirability, in view of the almost complete lack of toxicity of these substances.

## AMINO ACID DEFICIENCIES AND TOOTH DEVELOPMENT

The effects of several nutritional deficiencies and of a variety of endocrine imbalances upon dental development have been studied (I. Schour and M. Massler, "The Rat in Laboratory Investigation," Edited by E. J. Farris and J. Q. Griffith, *Ed. 2, Chapt. VI, pp. 104-165, J. B. Lippincott Co., Philadelphia, Pa. (1949)*). Heretofore the relation of amino acid intake to dental development has not been investigated.

H. A. Hunter (*J. Dent. Res.* **29,** *73 (1950)*) has reported an experiment with rats in which the effect of methionine deficiency, of lysine deficiency, and of total protein deficiency on incisor formation and eruption was studied. Eight groups, each of which was composed of 4 female albino rats weighing between 199 and 225 g., were maintained for thirteen weeks on dietary regimens differing in amino acid composition and in the amount of calories supplied daily.

Group 1 was fed a diet with the sole source of nitrogen being supplied by a mixture of fifteen amino acids without the essential amino acid, methionine; otherwise, the diet was believed to be adequate. Group 2 was fed the same type of diet with ample methionine but with lysine omitted. The rats in both of these groups were allowed to consume their diets without restriction. Group 3 was fed the same type of diet except that the amino acid mixture was replaced by casein at a 9 per cent level. Food intake in this group was restricted to the amount consumed by the rats in groups 1 and 2. Group 4 was fed the same basal diet completely devoid of any source of nitrogen. Group 5 was fed a laboratory chow with the caloric intake restricted to that of the previous groups. Group 6 was fed the 9 per cent casein diet ad libitum. Groups 7 and 8 were fed laboratory chow ad libitum in pellet form and in finely ground form, respectively.

The rats were weighed weekly and every other week they were anesthetized so that their rates of incisor eruption could be determined. The lower incisors were marked with a knife-edge abrasive stone at the margin of the free edge of the gingiva. The distance between the new and the last previous mark was measured (in millimeters) along the outer curvature of the incisor. At the end of the experiment, determinations of the hemoglobin and serum protein levels were made. Representative tissues were fixed for histologic study.

The average serum protein levels of the methionine-, lysine-, and protein-deficient groups were 4.80, 5.36, and 4.33 g. per 100 ml. of blood, respectively, compared with a value of 6.23 g. for the control group which consumed the 9 per cent casein diet with the caloric intake restricted. The hemoglobin levels of the three deficient groups were 14.0, 13.6, and 10.6 g. per 100 ml. of blood compared with a value of 14.6 g. for the same control group.

The rats fed the methionine-, lysine-, and protein-deficient diets all survived the experimental period but lost high percentages of their original body weights. The rats fed restricted amounts of the 9 per cent casein diet and the laboratory chow managed to maintain their original weights. The last three groups which were fed without restriction gained as much as 26 per cent of their original weights. Notwithstanding these extreme differences in ability to maintain or increase their body weights, there was no decrease in the rate at which the incisor of the deficient rats erupted. This was equally true for the early weeks of the experiments when the deficiencies were mild and in the latter weeks when 40 per cent or more of the original body weight had been lost.

When the rats were killed, representative lower incisors from the complete protein-deficient group (group 4) and from the group fed the 9 per cent casein diet ad libitum (group 6) were dissected and weighed. The incisors in group 4 were about 26 per cent

lighter than those in group 6. At the same time, the thickness of the incisors was determined at six representative areas. The diameters of the incisors from rats in group 4 were appreciably slighter than those in group 6.

The rate of eruption of the incisors is dependent upon the rate at which new tooth substance is elaborated; therefore, it appears that the normal processes of deposition of the organic matrices of enamel, dentin and cementum, and the calcification of these tissues, occurred almost unimpeded by the amino acid deficiencies. Thus, rate of growth of the rat and rate of eruption of the lower incisors seem to be independent of each other. However, the diameter of the incisor, and hence its weight, would appear to be to some degree related to the rate of growth of the rats. Probably the choice of the incisors of the rats in group 6 for comparison with those of rats in group 4 was an unfortunate one. Fairer controls for this purpose would have been the rats in group 3 which had been on a restricted caloric intake.

Histologic examination of the incisors from the methionine-, lysine-, and protein-deficient rats failed to reveal any pathology. The arrangement, proliferation, activity, and products of the odontogenic tissues appeared to be normal in all respects. Histologic study of the skeletal and cardiac muscles indicated an extreme atrophy of the myofibrils and proportionate increase in connective tissue elements. The livers of the depleted animals were remarkably regular with little evidence of degeneration. The spleens had smaller nodules with reduced lymphatic centers and little evidence of mitosis—essentially the appearance of subnormal lymphopoiesis. The ovaries of all animals showed a marked atrophy with few primary follicles and numerous degenerating follicles, but no intermediary stages.

The over-all picture in these animals is one of atrophy and mobilization of protein from the soft tissues in order to maintain the vital processes which require amino acids and protein formation. Apparently the tissue with the highest priority is the growing incisor. In many ways, this priority is readily understandable, for the incisor of the rat is not only his principal organ for obtaining food in particles small enough to masticate, but it also constitutes his first line of defense.

## EFFECT OF VITAMIN $B_{12}$ ON THE PAIN OF NEURITIS

The pathogenesis of so-called nutritional neuropathies remains a mystery. There is no clue as to why sensory rather than motor nerves are more liable to injury from dietary depletions, nor why feet and legs are affected more severely than knees or thighs. The role of thiamine in such neuropathies is the subject of much disagreement (C. D. Aring, J. P. Evans, and T. D. Spies, *J. Am. Med. Assn.* **113,** *2105 (1939)*; A. P. Meiklejohn, *New Engl. J. Med.* **223,** *265 (1940)*; *Nutrition Reviews* **6,** *157 (1948)*; **9,** *175 (1951)*).

Some neurologic changes which occur in association with pernicious anemia improve after therapy with vitamin $B_{12}$ (L. Berk, D. Denny-Brown, M. Finland, and W. B. Castle, *New Engl. J. Med.* **239,** *328 (1948)*; *Nutrition Reviews* **6,** *291 (1948)*). Because of this observation, W. B. Bean, M. Franklin and A. L. Sahs (*Am. J. Med. Sci.* **220,** *431 (1950)*) tried vitamin $B_{12}$ in the treatment of patients who had signs of peripheral neuritis and who complained of pains in the legs. For a one-week preliminary period of observation, during which time the patients were at rest in bed, they were given a diet containing only 200 micrograms of thiamine. The report concerns 3 of these patients, each of whom was given an intramuscular injection of 15 micrograms of concentrated vitamin $B_{12}$, and the subsequent improvement noted in their conditions. The results

were rather dramatic and were not recorded as a claim that the compound might have therapeutic value in other similar cases, but just because of the striking clinical results noted by the authors.

The first patient was a white man, 43 years of age, who had been a chronic alcoholic for many years and who had been admitted to the hospital because of paresthesias of the legs and feet of eight weeks' duration, and pain which had prevented him from walking. There were no signs of pellagra or cirrhosis. The feet and calves were tender to touch; the tendon reflexes were hypoactive, and touch and vibratory sensibilities in the legs and feet were decreased. The gait was unsteady.

On the seventh day of hospitalization, the patient was given an injection of 1 ml. of normal saline solution intramuscularly without apparent effect. The next day a similar injection containing 15 micrograms of vitamin $B_{12}$ was given. Thirty minutes later all spontaneous pain had vanished but the feeling of numbness remained. The neurologic examination was unchanged except that the pain and tenderness could not be induced and he could walk naturally. Within the next three days some pain had returned. Again a placebo of saline solution was of no value but 15 micrograms of vitamin $B_{12}$ once more brought relief.

The second patient was a 17-year-old school girl with marked pain, weakness, and numbness of all extremities, which had followed persistent nausea and vomiting of eleven weeks' duration. An absence of tendon reflexes and position sense in the legs and arms, tender skin and muscles, and weakness were noted. Administration of a saline placebo did not result in improvement, but 15 micrograms of vitamin $B_{12}$ induced rapid relief of pain, that is, within forty-five minutes. Some pain returned the next day.

The third patient, a man 58 years of age with a history of alcoholism and poor diet, had painful neuritis of the legs and feet which had grown worse for five years. Mild cirrhosis and fatty liver were noted. Again the placebo was without effect and administration of 15 micrograms of vitamin $B_{12}$ relieved the pain in one hour.

The response was so rapid that the effect appears to be a direct one and not a response to enhanced alimentary absorption. Similar dosages of vitamin $B_{12}$ were given intramuscularly to patients with poliomyelitis, to 4 patients with rheumatoid arthritis, 2 diabetics, 2 patients with multiple sclerosis, 2 with brachial neuritis, and one each with tabes dorsalis, trigeminal neuralgia, ruptured intervertebral disc, Korsakoff's psychosis, and monocytic leukemia. All of these patients had severe pain, apparently not on a nutritional basis, and none experienced any consistent improvement with the injection of vitamin $B_{12}$ or of normal saline. Two well-treated normal persons did not show any change in the pain threshold with the use of a Hardy-Wolff pain-inducing radiometer, after intramuscular injections of vitamin $B_{12}$.

These results give little insight into the mechanisms involved in nutritional neuritis, but the observations are clinically interesting and should stimulate further study.

## INFLUENCE OF SODIUM ON THE POTASSIUM REQUIREMENT

Workers at the University of Wisconsin have recently demonstrated that the requirement for potassium by rats is dependent upon the amount of sodium in the diet (R. R. Grunert, J. H. Meyer, and P. H. Phillips, *J. Nutrition* **42**, *609 (1950)*). They observed that the potassium requirement decreased as the sodium concentration in the diet was increased.

The dietary sodium and potassium levels tested ranged from 0.005 per cent of each (the level present in the basal diet) to 1.0

per cent of each. Male weanling rats weighing 40 to 45 g. were fed the diets for six weeks and the growth data were analyzed statistically. The minimum requirement for both sodium and potassium was established as the lowest level at which the average growth rate for 10 to 11 rats was not significantly different from the average maximum growth rate of an equal number of animals receiving any other dietary level of these elements.

The minimum sodium requirement was found to be 0.05 per cent of the diet during the first five weeks of the experiment and 0.03 per cent during the sixth week of the experiment. The sodium requirement remained unchanged when the amount of potassium ranged between 0.25 and 1.0 per cent of the diet.

During the first week of the experiment, the minimum potassium requirement was 0.18 per cent when the diet contained 0.1 per cent sodium, contrasted with a potassium requirement of 0.12 per cent when the sodium content of the diet was increased to 1.0 per cent. During the second week, the potassium requirements were 0.18 and 0.15 per cent with the low and high sodium intakes respectively. When the potassium content of the diet was below 0.09 per cent, the sparing action of sodium could not be demonstrated, and typical potassium deficiency symptoms developed.

The sparing action of sodium on the potassium requirement was demonstrable throughout the six-week experimental period although it gradually decreased and was nearly absent at the end of the period. The data indicated that the requirement for potassium decreased more rapidly with advancing age than did the sodium requirement. The potassium requirement, for example, had decreased to 0.09 per cent by the end of the sixth week (in the presence of 0.1 per cent dietary sodium), whereas the sodium requirement remained at 0.05 per cent during the first five weeks and then dropped to 0.03 per cent by the end of the sixth week (in the presence of 0.25 per cent dietary potassium).

The mechanism whereby increased dietary sodium improved the growth rate of rats fed less than the minimum requirement of potassium is not understood. The authors suggest that a shift of the two ions between the intra- and the extra-cellular phases of the body may be involved, and that sodium may be able to replace at least a part of the intra-cellular potassium. It has been demonstrated that sodium will replace the intracellular potassium in the muscle of the potassium-deficient rat (L. A. Heppel, *Am. J. Physiol.* **127,** *385 (1939)*), and also to some extent the potassium in red blood cells (A. H. Hegnauer, *J. Biol. Chem.* **150,** *353 (1943)*). Salt administration to human subjects after a period of salt deprivation results in a drop in urinary potassium excretion (*Nutrition Reviews* **8,** *69 (1950)*), which likewise is suggestive of a sparing effect of sodium on potassium.

The demonstration by the Wisconsin investigators that the potassium requirement is decreased with liberal intakes of sodium brings to mind the recent reports that the potassium requirement for growth in chicks is also decreased with liberal intakes of phosphorus (M. B. Gillis, *J. Nutrition* **36,** *351 (1948)*; **42,** *45 (1950)*). It has thus been established that the potassium requirement can be influenced by at least two other elements.

## VARIABLE RESPONSE TO DIETARY DEFICIENCIES IN CHICKENS

That animals of a given population vary in their behavior with respect to nutritional influences is well known. The variability in a given population is sometimes referred to as biochemical individuality, and the researcher usually strives to select experimental sub-

jects from populations which are fairly uniform and possess a minimum of variability. Whether or not the variability in response to a specific nutrient is related to specific genetic factors has not been established.

By selection, W. F. Lamoreux and F. B. Hutt (*Poultry Sci.* **27,** *334 (1948)*) were able to demonstrate that two strains of White Leghorns chickens varied considerably in their susceptibility to riboflavin deficiency. These workers believed that genetic differences between the two strains were involved. That genetics was concerned with the utilization of riboflavin was considered a reasonable assumption because both strains gained equally in body weight when fed an adequate diet.

I. M. Lerner and F. H. Bird (*Poultry Sci.* **27,** *342 (1948)*) attempted to establish a strain of chicks of low riboflavin requirement. On the basis of their results they decided they might have been selecting for a high growth rate rather than for specific resistance to riboflavin deficiency.

A. C. Groschke, M. Rubin, and H. R. Bird (*Poultry Sci.* **27,** *302 (1948)*) made the observation that hatchability of fertilized eggs from different hens varied greatly. The hens were maintained on a diet deficient in vitamin $B_{12}$, at that time known as the unidentified factor of cow manure. Supplements of the unknown factor restored hatchability to normal among the low hatchability individuals. At that time it was not known whether the differences in the hatchability of the eggs of different individual hens were due to specific differences in the vitamin $B_{12}$ requirements. It was decided that these differences might reasonably also be related to individual variations in the efficiency of some general physiologic process. If the latter were the case, then individuals of the population might also exhibit a variable response to other nutritional deficiencies. Experiments were reported by R. J. Lillie, M. W. Olsen, and H. R. Bird (*Ibid.* **30,** *92 (1951)*) that substantiate the latter point of view.

Rhode Island Red pullets were fed a basal vitamin $B_{12}$-low diet of the following percentage composition: ground yellow corn, 57; soybean meal, 30; steamed bonemeal, 4.2; limestone flour, 2.3; manganized salt (6 per cent $MnSO_4 \cdot 4H_2O$), 0.5; iodized salt, 0.2; vitamin A and D oil (400 I.U. of vitamin D), 0.3; alfalfa meal, 5; and butyl fermentation solubles (500 micrograms of riboflavin), 0.5. Synthetic riboflavin was added at the rate of 5 mg. per kilogram of diet. Hatchability data were collected on each individual hen for a period of eight weeks. The hens were then divided into three groups on the basis of hatchability records. Group 1 consisted of those individuals with egg hatchability records of 85 per cent or over; group 2 were those with hatchability records between 70 and 84 per cent; and group 3 were those with hatchabilities of 69 per cent or below.

Hens from groups 1 and 3 were then placed into the following four lots: lot 1 received diet A, the positive control diet, (basal vitamin $B_{12}$-low diet supplemented with 5 per cent cow manure as a source of vitamin $B_{12}$); lot 2 received diet A with riboflavin omitted (riboflavin-deficient diet); lot 3 received diet A with manganized salt omitted (manganese-deficient diet); and lot 4 received diet A with cow manure omitted (vitamin $B_{12}$-deficient diet).

From the hatchability records accumulated over a six-month experimental period it was evident that hens which had previously shown a poor hatchability record (group 3) proved relatively susceptible to riboflavin deficiency and to manganese deficiency as well as to vitamin $B_{12}$ deficiency. For example, among the hens that had a previous poor hatchability record (group 3), hatchability declined from a control level (diet A) of 55 per cent to 40 per cent in the hens on the riboflavin-deficient diet, to 31 per cent on the manganese-deficient diet,

and to 42 per cent on the vitamin $B_{12}$-deficient diet.

In contrast, among the hens that had a previous good hatchability record (group 1), the hatchability remained essentially unchanged with riboflavin-, manganese-, or vitamin $B_{12}$-deficient diets.

Similar results were obtained in another experiment in which the diets were modified by increasing their content of bonemeal to 7 per cent. The difference between the hens of high and low hatchability was not due to a difference in their ability to benefit from consuming excreta since similar results were obtained when they were kept on wire-floored cages or on litter-covered floors.

It was thus concluded that the variation in hatchability of eggs from different hens in the original population was not related specifically to variations in vitamin $B_{12}$ requirement but rather to some general physiologic difference which affected the utilization of 3 widely different nutrients, namely riboflavin, manganese, and vitamin $B_{12}$. More extensive studies of this type are urgently needed before any definite conclusions can be drawn as to the inheritance of susceptibility to a dietary deficiency.

## THE PATTERN OF FAT TRANSPORT IN LYMPH

The value of fats as purveyors of available food energy and the importance of an intact fat-absorbing mechanism in the utilization of the lipid-soluble vitamins constantly focuses attention on the pathway and mechanism of fat digestion, absorption and transport. The importance of the lymph as a pathway of lipid transport has recently been discussed (*Nutrition Reviews* **8,** *300* (*1950*)). However, questions have been raised regarding the complete hydrolysis of food fats, the necessity of prior hydrolysis for absorption, and whether the lymph is an exclusive pathway for transport of glycerides and free fatty acids. Indeed, it was contended that whereas glycerides are absorbed into the lymphatics, free fatty acids enter the circulation by way of the portal vein (A. C. Frazer, *Physiol. Rev.* **26,** *103* (*1946*)).

In an attempt to show whether or not fatty acids fed as such are transported in a different manner than those fed as glycerides, a study was planned in which the lipids were given as Δ 10,12-linoleic acid or as Δ 10,12 trilinolein (R. Reiser and M. J. Bryson, *J. Biol. Chem.* **189,** *87* (*1951*)); in one case the conjugated trilinolein made up 30 per cent of the triglycerides, in the other, 30 per cent free conjugated linolinic acid was dissolved in Wesson oil. The percentages of the conjugated fatty acid in the ingested fat and the chyle fat were then compared and on this basis the conclusion relative to the mode of absorption was made. The thoracic duct of adult rats was cannulated and the animals were given glucose and salt solution for a day thereafter. Two grams of either of the foregoing lipid preparations were then administered by stomach tube, and the lymph was collected in succeeding twelve-hour periods. The lymph fat from the lymph was prepared for study by alcohol-ether extraction, and saponification, and the fatty acids were then dried and weighed. The final qualitative estimation was made spectrophotometrically using an iso-octane solution of the lipids.

It was observed at the outset that the concentration of the conjugated linoleic acid was consistently less in the lymph fat than in the administered fat whether it was given as the glyceride or as the free fatty acid. This was accounted for by dilution with endogenous fat or by oxidation of the polyunsaturated fatty acid prior to or during absorption. The net data on the comparison

of labeled fatty acid in the food and in the lymph showed that there was in the lymph as much or more Δ 10,12 linoleic acid when it was administered in the free form as when it was given as the triglyceride. This supports the view that fatty acids are absorbed by the same route whether fed in the free form or in the esterified form.

The mode of transportation of absorbed fat has been the subject of renewed study. That the thoracic and abdominal lymph channels are important pathways has been reaffirmed (B. Bloom *et al., J. Biol. Chem.* **184,** *1* (*1950*); *Nutrition Reviews* (*loc. cit.*)). However, the long-accepted view that phospholipids represent the form of transport of a large part of the absorbed fatty acids has been called into question (D. S. Goldman, *et al., J. Biol. Chem.* **184,** *727* (*1950*)). In this investigation injected $C^{14}$-labeled palmitic acid was recovered in the phospholipids of intestinal mucosa, kidney, lung, heart and skeletal muscle, but little, if any, was demonstrated in the plasma phospholipids.

In an effort to elucidate further the question of the participation of phospholipids in the transport of fat a recent study has been made of the lymph (B. Bloom, I. L. Chaikoff, W. O. Reinhardt, and W. G. Dauben, *J. Biol. Chem.* **189,** *261* (*1951*)). Adult male rats were given an adequate mixed diet. Under anesthesia, cannulas were introduced into the thoracic duct of 4 animals and into the intestinal lymphatics of 3. Within six hours the animals began to drink the 1 per cent sodium chloride solution provided and in twelve hours they ate the basal diet. Water was substituted for the salt solution when free flow of lymph was established. The labeled palmitic acid as the triglyceride was dissolved in corn oil and administered by stomach tube after lymph flowed freely and the clotting in the cannula had ceased. About 1 ml. of lymph could be collected in the course of an hour, and total cholesterol, total fatty acids and phospholipid fatty acids were determined on the sample.

In these fed, unanesthetized rats some 7 per cent of the total fatty acids of the lymph lipids was present in the phospholipid fraction. The absorption of the $C^{14}$-labeled palmitic acid ranged from 70 to 83 per cent in 5 of the rats and from 41 to 53 per cent in the other two. More than 90 per cent of the tagged palmitic acid which had been absorbed was recovered from the thoracic and intestinal lymph. However, less than 4 per cent of the $C^{14}$-labeled fatty acid had been incorporated into the phospholipid fraction. Likewise it was calculated that less than 2 per cent of the non-phospholipid fatty acids were present as cholesterol esters. It would appear from the foregoing account that neither phospholipid nor cholesterol ester is a quantitatively important vehicle for the transport of fatty acids in lymph.

## ABSENCE OF INTRINSIC FACTOR OF INTESTINAL JUICE

It has always been assumed that the intrinsic factor of Castle is produced solely by the stomach. It would, of course, follow that if the stomach were totally removed, pernicious anemia invariably would develop. During the past few years total gastrectomy has been performed many times throughout the country, and although in a few cases pernicious anemia has developed after surgery, it has been most uncommon. There are, however, many who feel that, if the patient lives long enough after total gastrectomy, pernicious anemia will develop. Nevertheless, it has never been satisfactorily explained why pernicious anemia does not develop immediately after total gastrectomy.

It has been demonstrated that intestinal extract and the duodenal juice of swine produce a hematologic response among patients who have pernicious anemia (E. Landboe-

Christensen and C. L. S. Bohn, *Acta med. Scandinav.* **127,** *116 (1947)*; E. Meulengracht, *Ibid.* **82,** *352 (1934)*).

M. Paulson, C. L. Conley, and E. S. Gladsden (*Am. J. Med. Sci.* **220,** *310 (1950)*) have studied the secretions of the upper portion of the intestinal tract of patients who have undergone total gastrectomy to determine whether this juice would produce a response when administered to patients with pernicious anemia in relapse. Three patients who had total gastrectomy for carcinoma of the stomach were studied; none of the three showed any evidence of pernicious anemia. The juice from the jejunum was obtained by Levine tube, and was aspirated during three to four hours. About 100 ml. of bile-stained fluid was obtained at each collection. The material was strained through gauze and kept in a frozen state until used.

The assay of the intestinal secretion for intrinsic factor was carried out by administering it to a patient with typical pernicious anemia in relapse. When administered, a portion was thawed, mixed with 200 g. of uncooked beef, acidified with hydrochloric acid to pH 3 and incubated at 37° C. for four hours. The material was then neutralized and fed to a patient with pernicious anemia. A total of 1,600 ml. of intestinal juice was given over six consecutive days. Daily counts of reticulocytes and other studies of the blood showed that the intestinal juice produced no hematologic remission.

This study shows that if the intrinsic factor is present at all in intestinal secretion, it is in too low a concentration to be employed as an extragastric source of intrinsic factor in the human being. It has been shown that the administration of large quantities of gastric juice obtained from patients with pernicious anemia and given to patients with pernicious anemia in relapse does produce some reticulocyte response (S. M. Goldhamer, *Am. J. Med. Sci.* **191,** *405 (1936)*). This, of course, would suggest that there is a low concentration of intrinsic factor even in the gastric juice of patients with pernicious anemia.

It has been assumed that the normal human stores enough intrinsic factor to maintain a normal blood picture for years even without his stomach. This may be strengthened by the above findings but is still conjectural.

## NUTRITIONAL SURVEY OF FACTORY EMPLOYEES IN BOMBAY

Studies of food consumption in India have repeatedly called attention to gross dietary inadequacies in agricultural groups and among urban populations of the lower economic strata (H. E. C. Wilson, B. Ahmad, and D. N. Mullick, *Indian J. Med. Res.* **24,** *161 (1936)*; W. R. Aykroyd and B. G. Krishnan, *Ibid.* **25,** *1 (1937)*; D. D. Mitra, *Indian Med. Gaz.* **74,** *226 (1939)*; *Nutrition Reviews* **7,** *252 (1949)*; **8,** *334 (1950)*). Clinical manifestations of malnutrition and of deficiency diseases occur commonly (*Nutrition Reviews* **6,** *157, 181 (1948)*).

A nutritional survey was made of a group of factory workers and their families in Bombay during a period of rationing in 1947. The information accumulated was summarized and published in a recent report (E. R. DeMello, C. J. Modi, M. P. Walsh, and J. C. Patel, *Indian J. Med. Sci.* **4,** *337 (1950)*). Data on food consumption are given, as are the results of physical examinations and laboratory determinations.

There were 29 Hindu families, including 158 individuals, in the group studied. Twenty-three families included male factory workers engaged in heavy manual labor, while 6 families were those of individuals who worked in offices with lighter duties requiring much less expenditure of energy.

Food consumption of each family was determined during a period of seven consecu-

tive days. One of the investigators visited the home twice daily to weigh each item of food to be included in the diet of that day. Allowance was made for the loss of a given proportion of the food in wastage and in preparation. Food intakes were calculated on the basis of the number of consumption units included in the family, the consumption unit apparently being equivalent to that of the adult male.

Like the diets of many of the Asian people, those of the families studied contained large proportions of cereals and legumes and relatively little meat, milk, vegetables and fruits. Caloric intakes were higher in the families of workers engaged in heavy manual labor than in those of the office workers since additional rations were permitted this group. The average caloric content of the diets in the first group of families was 3150 calories per consumption unit per day, and in the second group was 2030 calories per day.

Intake of protein averaged 80 g. per day in families of heavy laborers and 67 g. per day in families of sedentary workers. However, calories derived from protein made up less than 10 per cent of the total calories. These levels of intake compare with recommended international standards of 12 to 15 per cent of total calories as protein or with the Recommended Dietary Allowances of the National Research Council of 70 g. per day of protein. Protein sources of the diets of these Bombay families were found almost entirely in cereal foods. However, it was of some interest to note that the animal protein content of the diets of families of office workers was twice as great as that of the manual laborers.

Since the families represented were from low income groups it was to be anticipated that the fat content of the diets would be relatively low. Fat intake averaged about 50 g. per day per consumption unit in the families of the heavy laborers and 40 g. in the families of the office workers. In both groups, fat of animal origin made up only 20 per cent of the total fat.

Daily consumption of carbohydrate was relatively great and averaged 565 g. and 350 g. respectively in the families of manual workers and office employees. This persists as characteristic of diets of individuals of lower economic levels the world over, with chief caloric sources in the less expensive foods such as cereals and legumes.

The mineral content of the diet provided calcium in quantities of 1.3 g. and 0.7 g. per day and iron averaging 44 mg. and 30 mg. daily, with the lower content in each instance occurring in families of sedentary employees.

The diets of the employees undertaking heavy labor contained about 200 I.U. of preformed vitamin A and 1550 I.U. of carotene per consumption unit daily. This compared with 150 I.U. of preformed vitamin A and 1425 I.U. of carotene in the families of the office employees. There was wide variation in levels of intake of vitamin A between families, and the intake was greatest in those families which included green leafy vegetables in their daily diets.

The diets were shown to contain similar quantities of thiamine in the two groups, averaging 1.3 mg. and 1.4 mg. per day. Ascorbic acid intake was 64 mg. per day per consumption unit in families of heavy laborers and 51 mg. in those of office workers.

By western standards, these diets are deficient in their content of meat, milk, and fresh fruits and vegetables. Of the essential nutrients the most pronounced deficiency is in vitamin A. For health and optimal function the diets should probably contain additional ascorbic acid and animal protein as well as vitamin A.

In addition to the analysis of the dietary habits of the families, an appraisal of the nutritional status of individuals was made by physical examination and certain laboratory determinations. Of the total of 158 persons included in the families studied, physical examinations were done on 107. Since the groups studied are described as families, it is of some interest to note that there were only 13 adult females included in

the group examined as compared to 61 adult males. This preponderance of males is explained as due to a large number of unmarried young adult males and also to the shortage of housing accommodations in Bombay.

Noteworthy in the physical description of these individuals is their small stature and low average body weight. The average height of the adult males was only 64 inches and the average weight, 104 pounds. The average height of the women, 56 inches, was 8 inches less than that of the men, while the average weight of adult females was only 85 pounds. The authors infer that these values fall well below usually used standards for height and weight in India and do not permit comparison either with foreign populations or with standards adapted for use with Indian populations of higher income groups, such as those provided by the insurance companies of that country. Although it is not stated in the paper, one could presume quite reasonably that the quantitatively and qualitatively poor diet consumed by these families was a factor in producing the low average height and weight.

Clinical manifestations of nutritional deficiencies were sought under criteria provided by the Nutrition Research Laboratories at Coonoor. Few such manifestations were found. Most notable, perhaps, was the occurrence of xerophthalmia in 10 individuals from 2 families. In addition there was evidence of stomatitis in 8 persons, all of whom also had parasitic infections. Rickets was found in one case. It can be concluded that signs of nutritional deficiency were not common in these subjects.

Red blood cell count, hemoglobin, and leucocyte count were determined on capillary blood. Although the average number of red blood cells was found to be slightly below the normal Indian standards for all age and sex groups, concentrations of hemoglobin were within normal ranges except in boys between the ages of 2 and 18 years and in children under the age of 2 years.

Fecal examinations were done on 85 individuals. Of these, 63 were found to have evidence of protozoal or parasitic infection. Anemia and clinical manifestations of nutritional deficiency occurred more commonly in persons with organisms in their feces than in those without such infections.

The diets consumed by these families of factory employees with low income in Bombay are not optimal and can be considered to be inadequate in their content of vitamin A and animal protein. Since the study was undertaken during a period of food rationing, it is wholly conceivable that the average diet of these individuals is actually improved over periods in which rationing is not in force. The small stature of the people may represent the result of long-continued consumption of inadequate or marginal diets. In addition, the common occurrence of parasitic infections may be related to poor nutrition. Other evidences of nutritional deficiency did not occur commonly. However, it may reasonably be proposed that the improvement of diets of factory workers in India would very likely result in economic gains of increased production and better worker health.

## BLOOD PYRUVATE CONCENTRATION IN LIVER COMA

A sizable proportion of patients dying with severe liver disease have a terminal stage of coma which is often of several days duration. The comatose state is sometimes heralded by a brief or even prolonged period of excitement and usually ends fatally. A search for the cause of the coma has not led to conclusive results and when biochemical changes in the blood have been sought, few of significance have been found. Thus, in spite of

the importance of the liver in intermediary metabolism, specific and consistent changes in the blood content of non-protein nitrogen, carbon dioxide, sugar, bilirubin, and prothrombin have not been evident. Moreover, the concentration of amino acids and of phenols, the latter possibly related to faulty intermediary metabolism of amino acids, has not been significantly or consistently altered in the comatose state. Finally, these patients are regularly treated with intravenous glucose and B-complex vitamins without any apparent effect upon the comatose state.

D. S. Amatuzio and S. Nesbitt (*J. Clin. Invest.* **29,** *1486 (1950)*) have confirmed an observation made by A. M. Snell and H. R. Butt (*Tr. Assn. Am. Phys.* **56,** *321 (1941)*) that the blood pyruvate concentration may be increased in patients with hepatic coma.

Thirty-five patients were studied, all with liver disease. They were maintained on a diet furnishing 3000 calories, including 150 g. protein daily, and were also given vitamins parenterally, including 110 mg. of thiamine, 100 mg. ascorbic acid, 10 mg. vitamin K, 5 mg. pyridoxine, 50 mg. pantothenic acid and 250 mg. of niacin. Of these 35 patients, 12 developed coma and were maintained during the comatose state on 3000 calories given by gastric intubation. No note is made of the protein content of the intubation formula.

Blood and spinal fluid values for pyruvic acid in a large control group were 1.04 and 1.02 mg. per cent respectively. There was no increase in pyruvate in the patients with liver disease except when greatly impaired hepatic function was observed. For example, 15 patients with decompensated portal cirrhosis had fasting blood pyruvic acid values of between 1.28 and 2.0 mg. per cent. The blood pyruvate concentration in these patients varied from 1.7 to 4.85 mg. per cent with a mean concentration of 2.65 mg. per cent. Likewise, the spinal fluid concentration was elevated to values from 1.54 to 2.35 mg. per cent. Two patients with severe liver disease were followed before and during coma. A progressive rise in blood pyruvic acid concentration was noted before the coma began, and sharply increased in the two days of the comatose state. Another patient with homologous serum jaundice had a marked increase in blood pyruvate on admission, when he was in a comatose state. This dropped to roughly normal values as the coma cleared and showed a transient rise again when he became drowsy for a second time. As the drowsiness cleared, the pyruvate concentration returned to normal.

Anoxia was eliminated as a cause of increased blood pyruvate concentration by the finding of normal blood pyruvate values in 12 patients with pulmonary emphysema, with arterial oxygen saturations of from 51.1 to 93.3 per cent.

The mechanism of the increased blood pyruvate concentration in these patients was discussed. Simple vitamin deficiency could not seem to account for the phenomenon since these patients were given large quantities of the vitamins concerned. The authors suggest that there might be a failure in the liver to assimilate pyruvate and to form dicarboxylic acids. In spite of the intake of thiamine, it is not impossible that the active coenzyme form, cocarboxylase, was partially lacking. In this connection, R. H. Williams and G. W. Bissell (*Arch. Int. Med.* **73,** *203 (1944)*) observed a diminished phosphorylation of thiamine in patients with severe liver cirrhosis. A diminished ability of the damaged liver to synthesize the apoenzyme (protein) might also be considered.

## UTILIZATION OF VITAMIN A AND CAROTENE BY THE RAT

Depending upon the diet and mode of administration, β-carotene has been reported to be from less than one-half to the equal of vitamin A alcohol in growth-promoting potency for the rat. The lower values were, for the most part, obtained before the critical role of tocopherols in the utilization of the carotenes was appreciated. Equal potencies of β-carotene and vitamin A were observed when fed with adequate amounts of α-tocopherol (1 mg. per rat per day) to rats on a low fat ration (C. J. Koehn, *Arch. Biochem.* **17,** *337 (1948)*; *Nutrition Reviews* **6,** *281 (1948)*).

The effect of tocopherol on the response to carotene, and the effects of the simultaneous presence of fats, "Tweens", and mineral oil in the ration on the relative potencies of carotene and vitamin A, have now been described in two papers by M. J. Burns, S. M. Hauge, and F. W. Quackenbush (*Arch. Biochem.* **30,** *341, 347 (1951)*). Using a diet containing casein, glucose, minerals, synthetic vitamins and 5 per cent of lard, they first determined the effects of variation in the level of α-tocopherol on the growth response to a supplement of one microgram daily for six weeks of either β-carotene or vitamin A (as vitamin A acetate). With no added tocopherol or with a level of 0.5 mg. per rat per day, vitamin A appeared definitely superior to β-carotene in growth-promoting action; however, when 1.0 mg. of the tocopherol was fed per day, there was no significant difference between the activity of the two supplements. A larger dose of α-tocopherol (2.0 mg. daily) again diminished the response to β-carotene as compared to vitamin A. The 1.0 mg. level of tocopherol thus appeared optimum for utilization of carotene. With tocopherol supplied at this level, it was next determined that dispersal of vitamin A in water with Tween 40 (sorbitan monopalmitate) slightly diminished its growth-promoting activity but enhanced that of the carotene. An equal amount of the Tween evaporated on the ration did not influence the activities of the supplements. When lard was removed from the ration (0.1 per cent of refined corn oil was then added), carotene and vitamin A still possessed equivalent growth activity, in confirmation of the results obtained by C. J. Koehn (*loc. cit.*) on a similar ration. However, the magnitude of the growth responses was less on the low fat ration than on the lard-containing ration. This was interpreted by the authors as a favorable effect of fat on the utilization of vitamin A and carotene. Equally likely, however, is the possibility that a growth response to the unidentified "lard factor"—which appears to have vitamin A activity under certain conditions (H. Kaunitz and C. A. Slanetz, *J. Nutrition* **42,** *375 (1950)*; *Nutrition Reviews* **9,** *165 (1951)*)—was involved.

The incorporation of small amounts of mineral oil into these diets resulted in a decrease in the efficiency of utilization of β-carotene. This effect was significant when as little as 0.08 per cent of mineral oil was present, and became very striking at levels of 0.16 to 0.32 per cent of mineral oil. At the latter level the response to 0.6 microgram daily of β-carotene was almost wholly eliminated (63.7 g. without mineral oil, 5.0 g. with mineral oil, at six weeks); that to vitamin A was slightly but significantly reduced (63.4 g. without mineral oil versus 51.6 g. with). These effects of mineral oil were not counteracted by increasing the lard content of the ration from 5 to 10 per cent. The authors point out that the amounts of mineral oil which show these deleterious effects are no larger than the amounts frequently employed in certain commercial feeds to reduce dustiness and prevent segregation of certain ingredients. Since much of the vitamin A of some feeds is supplied as carotene, the possible importance of the observation is obvious.

These observations reemphasize the many factors which influence the total vitamin A

potency of a feed or foodstuff. While the biologic methods of estimation in common use are undoubtedly of sufficient precision to afford an adequate guide to dietary vitamin A intakes, it should be evident that the numerical values recorded frequently give a false impression of the accuracy of our knowledge concerning the potency of a dietary supplement under conditions of practical nutrition.

## ARTIFICIAL ENRICHMENT OF WHITE RICE IN THE PHILIPPINES

A clinical survey conducted between October 1947 and February 1948 indicated that an average of 12.76 per cent of the human population of Bataan province in the Philippines either had frank beriberi or one or more symptoms indicative of the disease (J. Salcedo, E. O. Carrasco, F. R. Jose, and R. C. Valenzuela, *J. Nutrition* **36,** *501 (1948)*; *Nutrition Reviews* **7,** *90 (1949)*). These findings are consistent with observations and health records extending through many years. Beriberi has ranked second only to tuberculosis as a cause of death in the Philippines, the mortality rates being 141.91 and 168.23 respectively per 100,000 population in 1947.

Recently a second clinical survey was conducted between July 1949 and February 1950 (J. Salcedo *et al.*, *J. Nutrition* **42,** *501 (1950)*). The second survey illustrates the very striking improvement in the nutritional status of the Philippine population as a result of the rice-enrichment program, which was initiated, under controlled conditions, in October 1948.

The experiment was conducted in Bataan Province. Both a control area, where the ordinary rice of commerce was available, and an experimental area, where enriched rice was made available through usual retail channels, were included in the study. The experimental area had a population of approximately 65,000 and the control area, 29,000.

The enriched rice contained 2 mg. of thiamine, 16 mg. of niacin and 13 mg. of iron per pound. This is in accordance with the U. S. standard for enriched flour and corn meal. Riboflavin was omitted because it was thought that the yellow stain this vitamin would impart to the enriched grains might enable housewives to detect and discard them.

The enrichment pre-mix was supplied to the rice mills in the experimental area and inspections were made frequently in the mills, rice shops, and in the homes to insure that the enrichment pre-mix was used in proper amounts and that it was being used in the homes.

The results of the second survey indicated that after two years of rice enrichment the beriberi incidence had declined from 12.76 to 1.55 per cent of the population in the experimental area and to 8.7 in the control area. Furthermore, the severity of the disease diminished greatly in the experimental area so that cases of frank beriberi had almost disappeared. It was observed, on the other hand, that the severity of the disease actually increased in the control area for no known reason. A decline in beriberi incidence occurred in one control area, but this was traced to infiltration of enriched rice into 20 to 30 per cent of the homes in this municipality.

The beriberi mortality rate declined dramatically in the experimental area. During the year previous to enrichment the rate was 254 per 100,000 population annually and during the first year of enrichment it had dropped to 80 per 100,000. In the control area the rate remained essentially the same, 152 and 149 per 100,000 respectively before and after the experiment.

Infant deaths from beriberi declined 52 per cent during the first year of rice enrichment in the experimental area. In the control area, during the same period, the infant

deaths from beriberi increased 5 per cent. These data concerned nursing babies only, and the pronounced effect of enriched rice was therefore mediated chiefly, if not entirely, through improved maternal nutrition. The survey again emphasized that infantile beriberi is many-fold more prevalent than other forms of the disease. In 1947–1948 infant deaths were 88 per cent of all beriberi deaths in Bataan province.

Over-all mortality data were also tabulated. Tuberculosis, the most common cause of death in the Philippines, is a disease in which good nutrition is believed to have a favorable influence. It is of interest that the tuberculosis death rate declined in the experimental area from 306 per 100,000 population annually to 258 after enrichment. The corresponding figures for the control area were 253 and 265 respectively, or a slightly increased mortality rate from tuberculosis.

Changes in economic conditions were also carefully studied during the test period. Although there was a slight increase in the consumption of canned milk and a few small-scale relief deliveries of fish and other products, the authors estimated this source of food supply could not have amounted to more than one-half pound per person per year and thus could not have had any material effect on the rice enrichment program.

These results are indeed impressive and fortify the contention that enrichment of rice is an effective means of eliminating endemic beriberi in rice-eating populations.

## HEXOSAMINE LEVEL IN LUPUS ERYTHEMATOSUS

Acute disseminated lupus erythematosus is a progressive, systemic, usually fatal disease which is characterized by striking changes in the amorphous ground substance of tissues. This ground substance has been identified by histochemical technics as consisting largely of hyaluronic acid and chondroitin sulfuric acid.

Since hexosamine constitutes approximately 40 per cent of each of these mucopolysaccharides and since serum contains appreciable amounts of bound hexosamine (glucosamine and galactosamine) N. F. Boas and L. J. Soffer (*J. Clin. Endocrinol.* **11,** *39* (*1951*)) studied the circulating hexosamine in 19 patients with acute disseminated lupus erythematosus.

In 17 of the 19 patients the serum hexosamine level was increased above the normal range of 85 to 138 mg. per cent. In approximately one-half of the patients the levels were increased to over 200 mg. per cent. Eleven of the patients were treated with either ACTH or cortisone and the serum hexosamine level invariably fell with such therapy. When the dosages of these hormones were reduced to clinically ineffective levels, the hexosamine level invariably increased, to fall again when the dosages were increased. Thus the level of circulating hexosamine could be altered at will by modifying the treatment dosage schedule.

The initial fall in hexosamine level following ACTH or cortisone therapy developed in three to seven days.

Interpretation of these results is difficult since little is known of the source, function, metabolism or fate of hexosamine compounds. Hexosamine is a constituent of mucoproteins and its estimation is a rough index to changes in the total mucoproteins. As such it is probably related to the depots of mucopolysaccharides throughout the body such as cartilage, ground substance, mucous glands, vitreous humor, skin and blood vessels.

C. Ragan and co-workers (*Bull. N. Y. Acad. Med.* **26,** *251* (*1950*)) have recently observed in rabbits that wounds under the influence of ACTH and cortisone do not heal properly. The treated animals were unable to deposit ground substance and mucopoly-

saccharides in the healing wounds. This may in part explain the systemic improvement in lupus produced by these hormones since in this disease amorphous ground substance is laid down in excessive amounts. This is, however, speculative.

It should be pointed out that elevation of the serum hexosamine levels is not peculiar to disseminated lupus erythematosus, since it is elevated in many chronic disorders such as carcinomatosis, Hodgkin's disease, leukemia, rheumatoid arthritis, periarteritis nodosa, rheumatic fever and chronic infections. It also rises in acute illnesses such as pneumonia, acute myocardial infarction, experimental infections, and trauma. Thus the increase in hexosamine level, like the increase in sedimentation rate, fibrinogen, alpha globulins, gamma globulins, mucoproteins, and polysaccharides, is not specific for any one condition but rather appears to be a temporary response called forth by tissue injury and persists as long as the injury is present. This response has been variously interpreted as indicating tissue destruction or tissue proliferation. More fundamental knowledge will be required before the interpretation of these changes in reference to disease processes and their response to therapy can be understood.

## AMINO ACID REQUIREMENTS OF GROWING SWINE

Although it has long been recognized that the quality of dietary protein for swine is of major importance, very few attempts have thus far been made to determine amino acid requirements for this species of farm animal. Recently two groups of workers, one at Cornell University, and one at Purdue University, have conducted studies concerned with the requirements of growing swine for individual amino acids.

The Cornell group demonstrated that methionine was indispensable in the diet of growing swine (J. M. Bell, H. H. Williams, J. K. Loosli, and L. A. Maynard (*J. Nutrition* **40,** *551 (1950)*). They also reported on the quantitative requirements for lysine (M. J. Brinegar *et al., Ibid.* **42,** *129 (1950)*) and for isoleucine (Brinegar, Loosli, Maynard, and Williams, *Ibid.* **42,** *619 (1950)*).

The Purdue group also investigated the lysine requirement (E. T. Mertz, D. C. Shelton, and W. M. Beeson, *J. Animal Sci.* **8,** *524 (1949)*; *Arch. Biochem.* **30,** *1 (1951)*) and the methionine requirement (*J. Animal Sci.* **10,** *57 (1951)*). They reported further that tryptophan was indispensable (*Science* **107,** *599 (1948)*) and established the quantitative requirement for this amino acid under specified conditions (*J. Animal Sci.* **8,** *629 (1949)*; **10,** *73 (1951)*).

The quantitative requirement for methionine for growing swine was indicated by the Cornell study to be somewhere between 0.07 and 0.27 per cent of the diet when the latter contained 10 per cent of protein in the form of soybean meal. The Purdue group found that the methionine requirement was related to the total sulphur amino acid intake as follows: When a diet was fed containing 21 per cent protein (oxidized casein, gelatin, and tryptophan), the DL-methionine requirement was 0.6 per cent of the diet in the absence of cystine and 0.3 per cent in the presence of adequate L-cystine (0.3 per cent or more).

The requirements for L-lysine reported from the two laboratories were not in strict agreement, although the differences were not great and are perhaps explainable on the basis of strain difference and differences in the basal diet employed. The Cornell study indicated that when growing pigs were fed a diet containing 10.6 per cent of protein (linseed meal protein supplemented with methionine and histidine), the L-lysine requirement for normal growth was 0.6 per cent of the diet. When the basal diet contained 22 per cent of protein (sesame meal protein supplemented with methionine and histidine, or meat scraps, zein, and wheat sup-

plemented with methionine, histidine and tryptophan), the L-lysine requirement was 1.2 per cent of the diet. The Purdue workers found the L-lysine requirement to be 1.0 per cent of the diet when the latter contained 23.8 per cent protein (zein and gelatin supplemented with tryptophan, methionine, and histidine).

The DL-tryptophan requirement was reported by the Purdue group to be 0.2 per cent of the diet when the latter contained adequate niacin and 24.5 per cent protein (zein and gelatin supplemented with methionine, lysine, and histidine).

The L-isoleucine requirement was reported by the Cornell workers to be 0.7 per cent of the diet when the latter contained approximately 22 per cent of protein (blood flour supplemented with methionine).

The Cornell studies have emphasized the importance of considering the level of dietary protein in evaluating the individual amino acid requirements of growing swine. Their results with lysine indicate a direct correlation between the level of protein intake and the amino acid requirement. Expressed in another way, their result indicates that the L-lysine requirement is equal to approximately 5.5 per cent of the dietary protein.

The data accumulated on the amino acid requirements of growing swine, although incomplete, permit a comparison with the results obtained by W. C. Rose with the growing rat (*Science* **86,** *298 (1937)*). The values reported for growing swine for tryptophan (0.2 per cent), methionine (0.6 per cent), and lysine (1 to 1.2 per cent) are the same as those reported by Rose for the rat, whereas the requirement for isoleucine by swine (0.7 per cent) is higher than that reported by Rose for the rat (0.5 per cent).

Recent results from the Purdue laboratory indicate that swine can be grown successfully on diets containing an amino acid mixture as a source of protein (D. C. Shelton, W. M. Beeson, and E. T. Mertz, *Arch. Biochem.* **29,** *446 (1950)*). Weanling pigs were fed a diet containing 10 amino acids (those essential for rat growth) and diammonium citrate as the only nitrogen sources. Such a diet produced satisfactory growth. The essential nature of threonine was demonstrated by the reduction in growth that resulted when this amino acid was omitted from the mixture.

## THE WEIGHT CURVE OF CONGOLESE CHILDREN

During recent years and largely because of the impulse given by the Nutrition Divisions of the specialized agencies of the United Nations, considerable attention has been given to the nutritional problems of underdeveloped countries. This has been further emphasized by the development of the "Point Four" programs of technical assistance.

From the point of view of nutrition, Africa has remained largely, as has been aptly remarked, "terra incognita." Even population and anthropologic data are lacking for many territories. The botanical inventory of vegetables eaten daily by many African peoples has not yet been established. Properly conducted dietary surveys and man assessments of dietary surveys have been rare. While certain widespread syndromes of nutritional inadequacy, like Kwashiorkor (*Nutrition Reviews* **8,** *55, 161 (1950)*), are beginning to be known, many others probably are awaiting description. As in experimental nutrition, however, objective nutritional criteria have to be evolved if an integrated study is to be made of African malnutrition. Height-weight data, both for children and for adults, represent such incontrovertible criteria. The urgency of the need for height and weight statistics in Africa was therefore repeatedly emphasized during the first International Conference on African Nutrition, held in Dschang (French Cameroons) in October, 1949. A recent study made in the Belgian Congo (M. Brou, *Ann. Soc. Belg. Med. Trop.* **30,** *349 (1950)*) gives an example of the valuable lessons which can be derived from properly established weight curves.

The author was working in a region where births are generally recorded correctly. An almost insurmountable difficulty prevalent in many areas of Africa was thus avoided at the outset. Furthermore, this region—Bagata—is fortunate in having a well-organized system of postnatal care, which according to Brou covers almost all children up to the age of three years. All children could thus be seen once a month, which allowed for 36 weight determinations during the period of study. Between 600 and 700 children were followed. The author makes no comment on the ethnologic distribution of the native population. It may therefore be assumed that either the population of Bagata is more homogeneous than is customary in that region or, more likely, that no significant difference was found between weights of children of different origin.

The weight curve of the children showed marked deviations from the western average. While the first three months corresponded to a normal, regular, linear increase, a slowdown occurred during the fourth month. This was followed during the next four months by a period characterized by a plateauing of the average weight curve, considerable differences among children at a given age, and disorderly variations of the curve for individual children. The plateauing continued, with somewhat decreased individual variations, until the end of the first year: the average weight at twelve months, equal to the average weight at nine months, was found to be only about 15 pounds. During the first four months of the second year, a slow increase of weight (on the average, about 2 pounds) took place. The weight curve then became more regular and paralleled "normal" weight curves, while staying constantly below it. At three years the average weight was 25 pounds. The ratio then obtained between native and western weights is, according to the author, maintained during the rest of the growth period and even during adult life.

The nutritional interpretation of the accidents of the growth curve is easily done if dietary data are examined. During the first three months (period of normal growth), children are exclusively breast-fed. The fourth month corresponds to the introduction, in the diet of the child, of a manioc gruel of low protein, mineral and vitamin content. An immediate fall in the rate of growth follows. During the rest of the first year, maternal milk becomes a negligible component of the diet of the child, while manioc becomes the staple food. Depending on whether cachexia or edema prevails, low or relatively higher weights are recorded, the average staying almost constant. It is this period which has been shown by the students of Kwashiorkor to correspond to fatty infiltration of the liver, various dermatitis, and often irreversible processes such as cystic fibrosis of the pancreas. Mortality is high. The beginning of the second year, still essentially characterized by a manioc diet, but sometimes supplemented by other vegetables of higher biologic value, corresponds to the beginning of a rise in the weight curve, followed by a more regular, although still inadequate, growth.

Insofar as information is available, it seems that this weight curve of the Bagata children is fairly typical of Africa as a whole. Analogous weight curves have also been described in other "underdeveloped" areas. In all cases it may be presumed that the sudden replacement of the proteins of maternal milk, abundant and of high biologic value, by a small amount of vegetable protein of poor quality is the single most important cause of the abnormalities of growth. Other factors, such as the concomitant lack of calcium and vitamins, may also contribute to the disorder. It is therefore natural that the problems of protein nutrition during the immediate post-weaning period have recently come to be considered first in order of urgency by FAO and WHO. It is to be hoped that, as a result of these efforts, nutrition formulas of sufficient biologic value, which can be prepared from locally available foodstuffs, can be evolved and their use disseminated by proper educational methods.

# NOTES

## Conference on Nutrition Problems in Latin America

The conference on "Problems of Nutrition in Latin America" held in Montevideo, in July 1948, recommended that further conferences be held to follow up the work of this group. The report of the second conference, held in Rio de Janeiro, Brazil, during the summer of 1950, has now been published by the Food and Agriculture Organization of the United Nations (*FAO Report, Washington, D. C. (1950)*).

The conferences were attended by nutritionists from most of the countries in Latin America as well as by representatives of FAO, WHO, UNESCO, the International Labor Office, and many other international bodies. After a general review of problems of nutrition and current activities in the field throughout the region, the conference was divided into a number of committees which considered in detail an agenda concerned both with nutrition research and practical nutrition programs.

Special attention was devoted to the training in nutrition of professional workers, such as rural schoolteachers, welfare workers, agricultural technicians, and rural district nurses, who come in contact with "underprivileged rural groups." The methods of mass feeding of children of school age, applicable to that region, came under critical review. The importance of proper nutrition programs for industrial workers, at a period when the industrialization of many Latin American countries is being actively furthered, was underlined and certain general recommendations to the governments were evolved. Attempts at standardizing methods of dietary surveys, mass assessments of nutrition status, and laboratory studies in surveys were noted and some practical recommendations were derived.

The subject of food analysis was not neglected. Arrangements were made to centralize relevant bibliographies at the Nutrition Division of FAO and to standardize analytical methods at the Institute of Nutrition of Central America and Panama (INCAP). Studies of possible substitutes for whole milk were recommended.

The problem of endemic goiter, so prevalent in Latin America, was examined. Arrangements were made for the World Health Organization to cooperate with national governments in the solution of problems associated with iodinization of crude salt.

The importance of nutrition education was recognized by the attention devoted to methods of education of health workers, as well as to programs concerning children and adults.

Training of research personnel, both in the region and abroad, organization of symposiums, and strengthening of existing nutrition institutes also received attention.

The breadth of this report, the earnestness of its tone, and the thoroughness with which each point was covered indicate how "nutrition conscious" Latin American countries have become.

## Recent Nutrition Books

*Teaching Better Nutrition—A Study of Approaches and Techniques.* Food and Agriculture Organization of the United Nations, Washington, D. C. November 1950. Pp. 148. Price: $1.50.

*James Lind, Founder of Nautical Medicine.* Louis H. Roddis. Henry Schuman, Inc., New York 21, N. Y. 1950. Pp. 177. Price: $3.00.

*Table of Food Composition for the Armed Forces.* Annabel L. Merrill and Bernice K. Watt. United States Department of Agriculture. Pp. 47. Distributed by the Quartermaster Corps.

*Annotated Bibliography of Vitamin E, 1940 to 1950.* Philip L. Harris and Wilma Kujawski. The National Vitamin Foundation, Inc., 150 Broadway, New York 7, N. Y. Pp. 184. Price: $3.00.

## CLINICAL NUTRITION BRIEFS

"A group of institutionalized feebleminded individuals, ranging in age from 6 to 29 years, free of epilepsy or other obvious neurologic involvements, were studied. The subjects were divided into the control group (N = 15) and the experimental group (N = 18), approximately equated on the basis of sex, age, and intelligence as measured by the Stanford-Binet test. For sixteen weeks the experimental subjects were getting 24 g. of monosodium glutamate daily. A battery of psychologic tests was administered before the treatment was instituted and again at the end of the experimental period. The findings indicate a lack of beneficial effect of glutamic acid on intelligence or performance capacity." (*Nutrition Reviews* **9,** *113* (*1951*), Glutamic Acid and Mental Functions.)

"On their return to Canada a group of Canadian soldiers who had been detained in Japanese camps some forty-five months recovered most of their lost weight and many actually became grossly obese. The over-all recovery was much less complete despite a good diet high in protein and supplemented with vitamin B-complex. However, it was expected that most of the symptoms would disappear within one year. The symptoms frequently encountered in the repatriates were easy fatigability, profuse perspiration without adequate cause, paresthesias, cramps in the calf muscles, visual complaints (poor vision ascribed to weakness of the intrinsic ocular muscles, optic neuritis, and optic atrophy), edema, cardiovascular and gastrointestinal complaints, and 'nervousness.' " (*Nutrition Reviews* **9,** *137* (*1951*), A Follow-Up Study of Canadian Repatriates from Japanese Prisoner-of-War Camps.)

"Blood analyses were made on samples from 202 persons, the majority (approximately 150) being young adult women, pregnant or lactating, who had symptoms of beriberi, and a smaller group (approximately 50) who were classified as normal. Results of analyses were reported for thiamine and hemoglobin in blood; for protein, ascorbic acid, and carotene in serum; and for thiamine in urine. Data were also obtained on the effect of daily doses of thiamine on the levels of this vitamin in the red blood cells." (*Nutrition Reviews* **9,** *141* (*1951*), Nutrition Survey and Tests in the Philippines.)

"The observations indicate that during the first days of life the newborn infant excretes quantities of thiamine, riboflavin, and niacin in excess of those ingested in the diet. However, by the fourth day the infant is retaining ingested thiamine and riboflavin and is, therefore, in positive balance for these vitamins. This is not true, however, for niacin. Excretion of this vitamin and its metabolites greatly exceeds the quantities ingested. This finding is not readily explained. Other evidence would indicate that the stores of niacin in the infant at birth are not great." (*Nutrition Reviews* **9,** *153* (*1951*), Metabolism of "B Vitamins" in Newborn Infants.)

"In evaluating fructose and invert sugar as sources of parenteral calories, it must be remembered that the rapid administration of parenteral sugar solutions for caloric purposes is rarely indicated. Moreover, the sudden increase in plasma volume which ensues can actually precipitate cardiac failure in patients in borderline cardiac compensation. Although the difference in tolerance rates between glucose and invert sugar may appear to be appreciable when the two are compared, the *caloric* difference is not impressive." (*Nutrition Reviews* **9,** *173* (*1951*), Parenteral Administration of Fructose.)